Docket No.: PC-0028 US

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

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By: _____ Printed: Lisa McDill

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Lasek et al.

Title: INTESTINAL PROTEINS

Serial No.: 09/729,454 Filing Date: December 4, 2000

Examiner: Yu, M. Group Art Unit: 1642

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed August 28, 2003, and received by the USPTO on September 2, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **320.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 24, 27, 28, and 31 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to **Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.)** (Reel 011343, Frame 0931) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 24, 27, 28, and 31
Claims allowed:	Claims 25, 26, and 37
Claims canceled:	Claims 1-21
Claims withdrawn:	Claims 22, 23, 29, 30, and 32-36
Claims on Appeal:	Claims 24, 27, 28, and 31 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. §1.116 filed July 29, 2003 has been entered for purposes of this appeal. See the Advisory Action, mailed August 21, 2003, indicating the Amendment would be entered upon filing of an appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to polynucleotides, comprising the polynucleotide sequence of SEQ ID NO:3, encoding a human intestinal protein (IP-1), comprising the amino acid sequence of SEQ ID NO:1 (Specification, e.g., at page 4, lines 1-10, and page 11, lines 11-30). Appellants' invention also includes polynucleotides comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:3, polynucleotides encoding polypeptides
comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1 (e.g., at page 13, lines 22 through page 14, line 24), polynucleotides encoding immunogenic fragments of SEQ ID NO:1, complementary polynucleotides (e.g., at page 4, lines 5-24), recombinant polynucleotides encoding polypeptides comprising SEQ ID NO:1, variants, or fragments thereof (e.g., at page 4, lines 17-18),

recombinant polynucleotides comprising the sequence of SEQ ID NO:3, host cells transformed with recombinant polynucleotides (e.g., at pages 17-19), and methods of making polypeptides encoded by the claimed polynucleotides (e.g., at pages 18-19 and 40-41).

The intestinal protein, encoded by polynucleotides of the invention, has chemical and structural homology to a rabbit intestinal protein (g1762; SEQ ID NO:32) (Specification, e.g., at page 12, lines 8-13, and Figure 3). In addition:

> IP-1 is 475 amino acids in length and has seven potential N-glycosylation sites at N29, N38, N47, N48, N92, N160, and N210; one potential cyclic AMP- or cyclic GMP-dependent protein kinase phosphorylation site at S265; seven potential casein kinase II phosphorylation sites at T66, T225, S268, S273, S340, T354, and S440; eight potential protein kinase C phosphorylation sites at S30, S49, S61, S152, S193, T298, S307, and S340; two potential tyrosine kinase phosphorylation sites at Y242 and Y424; and one RGD cell attachment sequence at R113. A signal peptide sequence is predicted from M5 to Q28. Transmembrane regions are predicted from M5 to V33 and Y163 to L179. As shown in Figures 3A, 3B, 3C, and 3D, IP-1 has chemical and structural similarity with rabbit intestinal protein (g1762; SEQ ID NO:32). In particular, IP-1 and the intestinal protein share about 64% identity, a predicted signal peptide, two transmembrane regions, one potential cyclic AMP- or cyclic GMP-dependent protein kinase phosphorylation site, four potential casein kinase II phosphorylation sites, six potential protein kinase C phosphorylation sites, and two potential tyrosine kinase phosphorylation sites. (Specification at page 12, lines 1-13)

The polynucleotides of the present invention are useful, for example, for toxicology testing, drug discovery, and diagnosis, prevention and treatment of colon disorders, particularly colon cancer, Crohn's disease, and ulcerative colitis.

(6) ISSUES

1. Whether the claimed naturally occurring variants according to claims 24, 27, 28, and 31, meet the written description requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

Issue 1 - Whether the claimed naturally occurring variants according to claims 24, 27, 28, and 31 meet the written description requirement of 35 U.S.C. § 112, first paragraph

The Final Rejection

Claims 24, 27, 28, and 31 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification contains "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The rejection alleges in particular that:

- Appellants have not described a representative number of polynucleotides that comprise the large genus of claimed polynucleotides.

A. The rejection of claims 24, 27, 28, and 31 is improper because the Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:3.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or

> well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:3 are specifically disclosed in the application (see, for example, pages 11-12). Variants of SEQ ID NO:3 are described, for example, at pages 13-14. Incyte clones in which the nucleic acids encoding the human IP-1 were first identified and libraries from which those clones were isolated are described, for example, at page 11, lines 14-19 and page 28, lines 28-30 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, on page 12, lines 1-16. Given SEQ ID NO:1 and SEQ ID NO:3, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 or SEQ ID NO:3 having 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:3. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

Additionally, the term "naturally occurring" is a well-known term in the art which Appellants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that a ***"naturally occurring"*** sequence as recited in claims 24 and 31 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of the human intestinal protein IP-1) and SEQ ID NO:3 (the polynucleotide sequence encoding IP-1), one of skill in the art would be able

to routinely obtain a polynucleotide encoding "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., pages 16-17 and Example VII at pages 34-37.

The Office Action of November 27, 2002 further asserted that the claims are not supported by an adequate written description because "[s]ince the genus includes a large number of unpredictable species, possession of only one species is not seen as sufficient to reasonably convey possession of the entire genus" (Office Action of November 27, 2002, page 7).

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA.

For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular
DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 31 recites chemical structure to define the claimed genus:

> 31. An isolated polynucleotide selected from the group consisting of: ...
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:3...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:3. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides

recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078, cited in the Office Action of November 27, 2002). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to intestinal proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as intestinal proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 475 amino acid residues). This variation is far less than that of all potential intestinal proteins related to SEQ ID NO:1, i.e., those intestinal proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of December 4, 2000. Much has happened in the development of recombinant DNA technology in the 23 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:3, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. The term "naturally occurring" is fully supported in the Specification as filed

Contrary to the Examiner's assertions, the Specification, as originally filed, provides adequate support for claiming polynucleotides encoding naturally occurring amino acid sequences having 90% sequence identity to SEQ ID NO:1. For example:

> "IP" refers to a substantially purified protein obtained from any mammalian species, including bovine, canine, murine, ovine, porcine, rodent, simian, and preferably the human species, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.
> (Specification, page 8, lines 14-16)

Clearly, this definition of IP-1 encompasses naturally occurring variants of SEQ ID NO:1 from different species. The Specification further describes the identification of variants of SEQ ID NO:3.

A probe may be designed or derived from unique regions such as the 5' regulatory region or from a nonconserved region (i.e., 5' or 3' of the nucleotides encoding the conserved catalytic domain of the protein) and used in protocols to identify naturally occurring molecules encoding the IP, allelic variants, or related molecules. The probe may be DNA or RNA, may be single stranded and should have at least 50% sequence identity to any of the nucleic acid sequences, SEQ ID NOs:3-29. Hybridization probes may be produced using oligolabeling, nick translation, end-labeling, or PCR amplification in the presence of a reporter molecule. A vector containing the cDNA or a fragment thereof may be used to produce an mRNA probe in vitro by addition of an RNA polymerase and labeled nucleotides. These procedures may be conducted using commercially available kits such as those provided by APB. (Specification, at page 16, lines 18-26)

Hybridization probes are also useful in mapping the naturally occurring genomic sequence. The probes may be hybridized to: 1) a particular chromosome, 2) a specific region of a chromosome, or 3) an artificial chromosome construction such as human artificial chromosome (HAC), yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), bacterial P1 construction, or single chromosome cDNA libraries. (Specification, at page 17, lines 20-24)

Naturally occurring or recombinant protein is purified by immunoaffinity chromatography using antibodies which specifically bind the protein. An immunoaffinity column is constructed by covalently coupling the antibody to CNBr-activated SEPHAROSE resin (APB). Media containing the protein is passed over the immunoaffinity column, and the column is washed using high ionic strength buffers in the presence of detergent to allow preferential absorbance of the protein. After coupling, the protein is eluted from the column using a buffer of pH 2-3 or a high concentration of urea or thiocyanate ion to disrupt antibody/protein binding, and the protein is collected. (Example XIV at pages 40-41)

In view of the foregoing evidence, Appellants submit that the rejection of claims 26, 29-31, and 34 on the grounds that there is no written support for "naturally-occurring" variants of SEQ ID NO:1 and SEQ ID NO:3 in the specification" is not only improper but also without merit.

(9) CONCLUSION

The written description rejections under 35 U.S.C. § 112, first paragraph, should be reversed based on at least the arguments presented above. The Examiner failed to base the written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the

claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,
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Enclosures:
Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998)

APPENDIX - CLAIMS ON APPEAL

24. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:1, and

c) an immunogenic portion of a polypeptide consisting of the amino acid sequence of SEQ ID NO:1 selected from the group consisting of:

i) an immunogenic portion consisting of contiguous amino acid residues 120 to 141 of SEQ ID NO:1, and

ii) an immunogenic portion consisting of contiguous amino acid residues 234 to 245 of SEQ ID NO:1.

27. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 24.

28. A cell transformed with a recombinant polynucleotide of claim 27.

31. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:3,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:3,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).